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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,191	03/11/2004	Russell G. Kerr	6818-58-2	5136

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,191	KERR ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 14-20 are pending.

In response to the restriction requirement mailed on 7/26/2006, Applicant has cancelled all previous claims which were directed to the inventions of Groups I (polypeptide) and II (polynucleotide). Applicant has now introduced new claims 14-20 drawn to a method of cyclizing a substrate with an elisabethatriene cyclase. In view of Applicant's cancellation of claims 1-13 and the fact that new claims 14-20 are directed to a single invention, the Examiner has construed Applicant's response as an election without traverse of an invention directed to a method of cyclizing a substrate with an elisabethatriene cyclase. Claims 14-20 are at issue and are being examined herein.

Specification

1. The specification is objected to for the following reasons. The first paragraph of the specification does not provide the current status of parent applications to which priority is claimed. Appropriate correction is required.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/351,984 filed on 01/25/2002.

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 10/351,766 filed on 01/27/2003.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 10/18/2004 is acknowledged. The reference by Ucciani et al. is not in conformance with MPEP § 609 and has not been considered for the following reasons. The instant reference is in French and Applicant has not provided an English translation. The remainder of the references in the IDS are in compliance with the provisions of 37 CFR 1.97. Accordingly, they are being considered by the examiner.

Drawings

5. The drawings submitted on 3/11/2004 have been reviewed and are accepted by the Examiner.

Claim Objections

6. Claim 16 is objected to due to the recitation of "3-PhGGPP". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

7. Claim 16 is objected to due to the recitation of "wherein the substrate is geranyl-geranyl diphosphate analogue". The term should be amended to recite "wherein the substrate is a geranyl-geranyl diphosphate analogue". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 14-20 are indefinite in the recitation of "elisabethatriene cyclase" for the following reasons. While the specification appears to disclose the term as referring to an enzyme which catalyzes the cyclization of a substrate to elisabethatriene, the art, as evidenced by Bruck et al. (Comparative Biochemistry and Physiology Part B 143:269-278, 2006) discloses an enzyme having the same enzymatic activity as an "elisabethatriene synthase". Thus, it is unclear as to whether the term "elisabethatriene cyclase" as recited in the claims is intended to also encompass the term "elisabethatriene synthase". For examination purposes, the Examiner will assume that the term reads "enzyme which catalyzes the cyclization of a substrate to elisabethatriene". Correction/clarification is required.

11. Claim 16 is indefinite in the recitation of "wherein the substrate is geranyl geranyl diphosphate analogue selected from the group consisting of: GGPP analogues..." for the following reasons. It appears that the abbreviation GGPP as recited in the specification stands for "geranyl geranyl diphosphate". Thus, the term "GGPP analogues", which is part of the recited group, is the same as the term "geranyl geranyl diphosphate analogue" recited in the preamble. For examination purposes, no patentable weight will be given to the term "GGPP analogues". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-19 are directed to a method of cyclizing any substrate, or selected substrates, with a genus of enzymes that catalyze cyclization of a substrate to elisabethatriene. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is no structural limitation with regard to the members of the genus of enzymes required by the claimed method or the genus of substrates to be cyclized. While the specification of the instant application partially discloses the structure of one species of the genus of enzymes recited, it provides no information as to the structural elements required in any enzyme which can cyclized any substrate, or the structural elements required in any substrate to be cyclized by the single enzyme disclosed. The specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality (i.e., cyclization of substrate).

The claims encompass a large genus of enzymes and substrates which are structurally unrelated. A sufficient written description of a genus of products may be achieved by a recitation of a representative number of products defined by their structure (e.g., amino acid sequence) or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of enzymes or substrates recited in the claims, and there is no information as to a correlation between structure and function. Furthermore, while one could argue that the single enzyme species disclosed is representative of the structure of all the members of the genus of enzymes recited, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the required enzymatic activity has been provided, one cannot reasonably conclude that the structures disclosed are representative of all the enzymes recited.

Due to the fact that the specification only discloses one species of the genus of enzymes required and a few substrates for the enzyme disclosed, as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

14. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cyclizing GGPP, GGPP analogues, 3-PhGGPP, FPP, FPP isomers, FPP

analogues, and phosphoisoprenoids with a polypeptide which (1) comprises SEQ ID NO: 1, 2, 3, 4, and 5, (2) has an isoelectric point of 5.1, (3) a molecular weight of 47 KDa, and (4) has the ability to cyclize geranyl geranyl diphosphate to elisabethatriene, does not reasonably provide enablement for a method of cyclizing any substrate, or selected substrates, with any enzyme that catalyzes cyclization of a substrate to elisabethatriene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 14-19 are so broad as to encompass a method of cyclizing any substrate, or selected substrates, with any enzyme that catalyzes cyclization of a substrate to elisabethatriene. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. The enablement provided is not commensurate in scope with the claims due to the potentially large number of enzymes and substrates of unknown structure recited in the claims. In the instant case, the specification enables a method of cyclizing GGPP, GGPP analogues, 3-PhGGPP, FPP, FPP isomers, FPP analogues, and phosphoisoprenoids with a polypeptide which (1) comprises SEQ ID NO: 1, 2, 3, 4, and 5, (2) has an isoelectric point of 5.1, (3) a molecular weight of 47 KDa, and (4) has the ability to cyclize geranyl geranyl diphosphate to elisabethatriene.

The amount of direction or guidance presented and the existence of working examples. The specification partially discloses the structure of a single enzyme having the recited enzymatic activity. However, the specification fails to provide any clue as to (1) the structures of other proteins having the same enzymatic activity as that of the protein of the instant application, (2) whether the partial fragments disclosed (SEQ ID NO: 1-5) are essential for enzymatic activity, either individually or as a set, (3) the structural elements required in any protein having the required functional characteristics, or (4) the structural elements required in any substrate that can be cyclized by the single protein disclosed or by any protein having the recited enzymatic activity. There is no information or guidance as to the amino acids in the enzyme disclosed which are associated with the recited enzymatic activity. No information has been provided as to the structural elements required in any substrate which can be cyclized with the enzyme disclosed or any protein having the recited functional characteristics.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any protein having the recited enzymatic activity. In addition, the art does not provide any teaching or guidance as to (1) which amino acids in the protein disclosed are essential for the enzymatic activity required, (2) which are the structural features required in any substrate that would be cyclized by the protein of the invention. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects

caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a protein were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for any number of proteins to determine which ones have the recited enzymatic activity. Furthermore, it is not routine in the art to isolate/create any protein with the activity recited without any knowledge as to the structural features which would correlate with that activity. In the absence of a correlation between structure and the required enzymatic activity, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have the ability to cyclize any substrate to elisabethatriene.

While enzymatic assays are well known in the art, the amount of experimentation required is not routine due to the fact that there is no limit as to the number of species to be tested, both enzymes and substrates. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

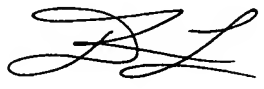
Conclusion

15. No claim is in condition for allowance.

16. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 7, 2006